24. The method of claim 23 wherein said sensitizer generates singlet oxygen upon photoactivation.

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25. The method according to 19, 20, 21, or 22 further including, prior to said step of electrophoretically separating, a step of separating said released eTag reporters from any components that interfere with electrophoretic analysis.--

REMARKS

Claims 1-4 have been cancelled and new claims 5-25 have been added. Claims 5-25 are currently pending in the application. All pending claims are set forth in Exhibit B with amendments shown (if applicable).

Attorney for Applicants gratefully acknowledges the interview with the Examiner on 12 July 2002 in which the rejections and the subject matter sought to be covered by the proposed new claims were discussed. The new claims have been submitted to more clearly describe Applicants' invention and to overcome rejections based on 35 U.S.C. 112 second paragraph.

As explained in the interview, the amendments to the specification are for the purpose of expressly incorporating passages from the parent application USSN 09/698,846 that were incorporated by reference in the instant application (page 1, lines 7-8). The passages inserted at page 4, line 10, were amended as indicated in Exhibit A to corrected typographical errors. Further corrections to the figure captions for Figures 4, 33, and 34 have been made to correct typographical errors.

In regard to the new claims, where basis for a term or phrase is found in the incorporated passages, the page and line numbers refer to the location in the parent application 09/698,846. (Such page and line references have the designation "('846)" in the right hand side of the box below).

Basis new claims are as follows:

New Claim(s)	Term/Phrase	Basis
5, 19	"antibody binding compound"	Page 33, Table 4. Page 8, line 15. ('846) Claim 38 of parent application ('846)
5, 19	"each antibody binding compound having one or more eTag reporters attached thereto by cleavable linkages"	Page 29, line 44, to page 30, line 6. Page 33, Table 4. ?
10	"[(M,D)-L]k-T" with k=1 to 20.	Claim 1 Page 30, line 1.

		Page 33, Table 4. Page 18, lines 7-8. ('846)
5, 19	"cleavable linkages"	Page 20, line 8, to page 22, line 27. ('846)
5, 19	" eTag reporters ... distinguished from those of other antibody binding compounds by one or more physical characteristics"	Page 8, lines 12-13. ('846)
5, 19	"complex formed"	Page 30, lines 27-34. Page 8, lines 17-20. ('846)
5, 19	"cleaving the cleavable linkages of each antibody binding compound forming such complex so that eTag reporters are released"	Page 8, lines 17-24. ('846) Page 33, Table 4.
5	"separating and identifying the released eTag reporters based on the one or more physical characteristics to determine the presence or absence of the plurality target compounds"	Page 29, lines 11-19. Page 43, line 5, to page 45, line 14. Fig. 8, 26, 27. Page 8, lines 22-29. ('846) Figs. 7. ('846) Page 10, lines 3-4 ('846)
19	"electrophoretically separating and identifying the released eTag reporters to determine the presence or absence of the plurality target compounds"	Page 4, lines 35-38. Page 43, line 5, to page 45, line 14. Page 8, lines 22-29. ('846) Figs. 2-9. ('846)
6	"separating" prior to cleaving.	Page 30, lines 14-17. Page 30, lines 27-34. Page 18, lines 12-14. ('846)
7, 15, 21	"cleavable linkages are each an olefin, a thioether, a sulfoxide, or a selenium analog of the thioether or sulfoxide"	Page 19, line 11. ('846) Pages 21-22. ('846)
8	"oxidizing"	Page 19, line 10. ('846)
9, 18, 23	"fluorescent label or electrochemical label"	Page 10, lines 16-25. Page 24, lines 19-25. ('846)
11, 16, 23	"from 5 to 100 antibody binding compounds"	Page 29, lines 22-24.
9, 14	"one or more physical characteristics are electrophoretic mobility or fluorescence"	Page 14, line 28, to page 15, line 2. ('846) Pages 22-29. ('846)
10	"1 to 500 atoms" in reference to M	Page 17, line 14.
12	"k is in the range of from 1 to 3"	Page 30, line 6.
13	"said plurality of antibody binding compounds is in the range of from 5 to 50"	Page 29, line 22-23.
10, 12, 17	"group consisting of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and boron"	Page 17, lines 16-17.
11	"distinct charge/mass ratio in the range of from –0.001 to 0.5"	Page 23, line 11.
8, 14, 20	"oxidizing said cleavable linkages" OR "cleavable linkage is cleaved by oxidation"	Page 19, lines 5-17. ('846)
14, 19	"second antibody binding compound	Claim 37 & 47. ('846)

	having a sensitizer for generating an active species"	Page 19, lines 19-29. ('846) Page 33, Table 4.
14, 19	"active species"	Page 18, line 16, to page 17, line 3. ('846)
12, 17	"1 to 300 atoms" in reference to M	Page 17, line 14.
14, 19	"sensitizer"	Page 19, line 31, to page 20, line 3. ('846)
22	"said binding compound and said second binding compound are each antibodies"	Page 33, Table 4.
24	"sensitizer generates singlet oxygen upon photoactivation"	Page 18, line 25. ('846)
25	"step of separating said released eTag reporters from any components that interfere with electrophoretic analysis"	Page 34, lines 34-44.

In regard to the above terms, it would be clear to one of ordinary skill in the art that an antibody binding compound may include one or more antibodies or components derived from antibodies, such as Fab fragments, secondary antibodies, or the like, or other ancillary components, such as biotins or streptavidin, or like components commonly used in the immunoassay art. Likewise, one of ordinary skill in the art would recognize that the distinctness of an electrophoretic peak could be based on either electrophoretic mobility or fluorescence, as disclosed on page 15, line 28, to page 16, line 2, of parent application 09/698,846.

No new matter has been added by the amendments. Reconsideration is respectfully requested.

Provisional Double Patenting

The Examiner provisionally rejected claims 1-4 under the doctrine of obviousness-type double patenting with respect to the following claims of the following copending applications:

Claims	Ser. No. of Copending Application
1-20	09/825,244
1-10	09/825,247
1-19	09/825,245
1-15	09/825,246
1-10	09/824,905
1-4	09/824,861
1-4	09/824,851

In view of the above amendments, Applicants respectfully disagree with the above rejection as it applies to copending applications 09/825,247; 09/825,245; 09/825,246; and 09/824,905, as the subject matter of these applications is directed to oligonucleotide binding compounds that bind to polynucleotide targets, whereas the subject matter of the present

application is directed to antibody binding compounds. Applicants submit that the binding events of the respective methods operate by different mechanisms and that the knowledge of one method by one of ordinary skill in the art would not render the other method and materials obvious.

Applicants have enclosed appropriate Terminal Disclaimers with respect to the above copending applications to overcome the above rejections. Accordingly, Applicants respectfully request that the above rejections be withdrawn.

Rejections Under 35 U.S.C. 112

The Examiner rejected claims 1-4 under 35 U.S.C. 112 second paragraph because of various instances of unclear language and lack of antecedent basis.

Applicants respectfully disagree with this rejection, particularly in view of the above amendments. The above terms no longer appear in the pending claims. Accordingly, Applicants request that the rejections by withdrawn.

Rejection Under 35 U.S.C. 102

The Examiner rejected claims 1 and 4 under 35 U.S.C. 102(b) as being anticipated by Grossman (5,470,705). The Examiner argues that Grossman discloses all the elements of Applicants' method, including the step of providing a binding polymer (presumably the rough equivalent of Applicants' "antibody binding compound"), a mobility modifying polymer chain (presumably the rough equivalent of Applicants' "eTag reporter"), and a detection moiety.

Applicants respectfully disagree, particularly in view of the amendments. The binding polymer of Grossman is limited to oligonucleotides or related analogs that bind to a target polynucleotide by hybridization (col. 6, line 56, to col. 7, line 30), and there is no disclosure or suggestion in Grossman of any other class of binding compounds. The "binding" elements of Applicants' composition are "antibody binding compounds" that are not related to oligonucleotides structurally, in the manner in which they are made, or in how they bind to their target compounds. Applicants' "antibody binding compound" element is not disclosed by Grossman. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Rejections Under 35 U.S.C. 103

The Examiner rejected claims 2-3 under 35 U.S.C. 103(a) as being unpatentable over Grossman (5,470,705) in view of Babon (5,851,770). The Examiner applies Grossman as described above. Babon discloses use of a capture ligand, such as biotin, to capture on a solid

phase support various hetero- and homoduplexes that may or may not contain mismatched basepairs. Captured duplexes are treated with a mismatch-recognizing nuclease that cleaves the captured sequences at mismatch locations to release fragments which are then analyzed by electrophoresis. The Examiner argues that it would be obvious to one of ordinary skill to modify the probes of Grossman to include the capture ligands of Babon, thereby obtaining Applicants' invention. One of ordinary skill would be motivated to make such a combination because of the advantages of being able to wash away unbound probe in the solid phase system disclosed by Babon.

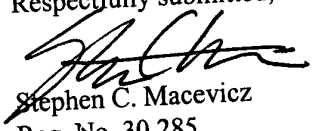
Applicants respectfully disagree, particularly in view of the above amendments. As the invention is presently described in the amended claims, neither nucleic acid binding compound nor capture agents are employed in the invention, and there is neither disclosure nor suggestions in the cited art that would lead one of ordinary skill in the art to the possession of Applicants' invention.

Accordingly, Applicants respectfully request that the above rejection be withdrawn.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and that the claims be allowed and the application quickly passed to issue.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **50-2266**.

Respectfully submitted,



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Enclosures:

Terminal Disclaimers for USSNs: 09/824,905; 09/825,245; 09/825,246; 09/825,247; 09/824,851; 09,/825,244; and 09/824,861.
Petition for Time Extension
CPA Request Transmittal form PTO/SB/29
Supplemental Information Disclosure Statement with cited references

Exhibit A
Amendments to the Specification showing Insertions and Deletions

Page 5, line 1 , with amendments shown:

--Methods and compounds are provided for multiplexed determinations, where the compounds can be linked to binding compounds for detection of reciprocal binding compounds in a sample. The methods are distinguished by having a plurality of binding events in a single vessel using a mixture of differentially eTag reporter [~~receptor~~] conjugated binding compounds, the release of identifying eTag reporter [~~receptor~~] of those binding compounds bound to their target compounds in the same vessel, and the detection of the released identifying tags by separation of the tags in a single run. The eTag reporter [~~receptor~~] are distinguished by having one or more physical characteristics that allow them to be separated and detected.

The method employs a mixture of binding compounds bound to eTag reporters, where each eTag reporter has a characteristic that allows it to be uniquely detected in a single separation run. The method involves combining the eTag reporter conjugated binding compound with a sample to determine the presence of a plurality of targets under conditions where the binding compounds bind to any reciprocal binding partners to form a binding complex. After sufficient time for binding to occur, the eTag reporters can be released from binding complexes in the same vessel. Various techniques are employed depending upon the nature of the binding compounds for releasing the eTag reporters bound to the complex. The released eTag reporters are then separated and identified by their differentiable characteristics free of interference from the eTag reporters still bound to the binding compound. The techniques for differentiating between eTag reporters bound to a complex and not bound to a complex, include enzymatic reactions that require the complex to exist for cleavage to occur, modification by using ligand/receptor binding, where the ligand is part of the binding compound, so that after cleavage, eTag reporter [~~receptor~~] still bound to the binding compound is modified, dual binding to the target resulting in release of the eTag reporter [~~receptor~~], where optionally eTag reporter [~~receptor~~] bound to the binding compound is modified, and the like.

One set of eTag reporters [~~receptors~~] are distinguished by differences, which include mass as a characteristic. These eTag reporters do not rely on differentiation based on oligonucleotides of 2 or more, usually 3 or more nucleotides, but rather on organic chemical building blocks that are conveniently combined together to provide for large numbers of differentiable compounds. Therefore, while the original eTag reporter or eTag reporter

conjugated to the binding compound can have 2 or more nucleotides, when released from the binding compound, the released eTag reporter will have not more than 3, usually not more than 2 nucleotides. Of particular interest are eTag reporters [~~receptors~~] that are characterized by differences in their mass/charge ratio. These compounds are distinguished by having differences in mobility and are characterized by having regions, which serve as (1) a cleavable linking region; (2) a mass-modifying region; (3) a charge-modifying region: and (4) a detectable region, where the regions may be separate and distinct or combined, there being at least two distinct regions that provide for the differentiation. These eTag reporters may be combined in kits and assays with compounds having all of the regions within a single region to further expand the number of different compounds used as eTag reporters in a multiplexed determination. These compounds find use with other compounds where the different regions are present in the same moiety, for example one to two regions, where the charge-modifying region may also be the detectable region or the mass-modifying region. By having a plurality of compounds that can serve as identifying molecules, mixtures of target compounds can be assayed in a single vessel. By using protocols that result in the release of eTag™ reporters from the binding compound that are identifiable due to differences in mobility, the analysis is greatly simplified, since the eTag reporters will be substantially free of interfering materials and their differences in mobility will allow for accurate detection and quantitation.—

Page 6 lines 13-14 with amendments shown:

--Figure 4 illustrates the design and synthesis of e-tags using [~~a LabCard (Detection: 4.7 cm; 200 V/cm) and~~] standard phosphoramidite coupling chemistry.—

Page 9, lines 6-7, with amendment shown:

--Figure 33 is a schematic diagram of the steps involved in the synthesis of the phosphoroamidite of biotin-deoxycytosine (dC)[~~(Reagent C)~~].—

Page 9, lines 8-9, with amendment shown:

--Figure 34 is a schematic diagram of the steps involved in the synthesis of the phosphoroamidite of biotin-deoxyadenosine (dA)[~~(Reagent D)~~].--

Page 38 lines 3-9, with amendments shown:

-- In one approach, the e-tag probe is constructed sequentially from a single or several monomeric phosphoramidite building blocks (one containing a dye residue), which are chosen to generate tags with unique electrophoretic mobilities based on their mass to charge ratio. The e-tag probe is thus composed of monomeric units of variable charge to mass ratios bridged by phosphate linkers. Figure 4 illustrates the design and synthesis of e-tags using [~~a LabCard (Detection: 4.7 cm; 200 V/cm) and~~] standard phosphoramidite coupling chemistry.[~~).~~] The separation of e-tags on a LabCard (Figure 5) has been demonstrated.--

Exhibit B
Currently Pending Claims Showing Amendments (if applicable)

--5. A method for determining the presence or absence of one or more target compounds in a sample, the method comprising the steps of:

providing one or more antibody binding compounds specific for a target compound, each antibody binding compound having one or more eTag reporters attached by cleavable linkages, the one or more eTag reporters of each antibody binding compound being distinguished from those of other antibody binding compounds by one or more physical characteristics;

combining with the sample one or more antibody binding compounds for each of the target compounds such that in the presence of a target compound a complex is formed between each target compound and the one or more antibody binding compounds specific therefor;

cleaving the cleavable linkages of each antibody binding compound forming such complex so that eTag reporters are released; and

separating and identifying the released eTag reporters based on the one or more physical characteristics to determine the presence or absence of the one or more target compounds.

6. The method of claim 5 further including a step prior to said step of cleaving, the step comprising separating said complexes from unbound said antibody binding compounds.

7. The method of claim 6 wherein said cleavable linkages are each an olefin, a thioether, a sulfoxide, or a selenium analog of the thioether or sulfoxide.

8. The method of claim 7 wherein said step of cleaving includes oxidizing said cleavable linkages to release said eTag reporters.

9. The method according to claim 5, 6, 7, or 8 wherein each of said eTag reporters has a fluorescent label or an electrochemical label, and wherein said one or more physical characteristics are electrophoretic mobility or fluorescence.

10. The method of claim 9 wherein said antibody binding compound is selected from a group defined by the formula:

$[(M, D)\text{-}L]_k\text{-}T$

wherein:

T is an antibody specific for said target compound;

k is an integer in the range of from 1 to 10;

L is said cleavable linkage;

D is a detection group; and

M is a mobility modifier consisting of from 1 to 500 atoms selected from the group consisting of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and boron; and wherein upon cleavage M and D impart on said eTag reporter a distinct mass/charge ratio so that said eTag reporters from different antibody binding compounds form distinct peaks upon electrophoretic separation.

11. The method of claim 10 wherein said mass/charge ratio is in the range of -0.001 and 0.5, and wherein said step of providing includes providing a plurality of from 5 to 100 said antibody binding compounds.

12. The method of claim 11 wherein k is in the range of from 1 to 3, and wherein M is a mobility modifier consisting of from 1 to 300 atoms selected from the group consisting of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and boron.

13. The method of claim 12 wherein said plurality of said antibody binding compounds is in the range of from 5 to 50.

14. The method of claim 5 wherein said cleavable linkage is cleaved by oxidation, wherein said one or more physical characteristics are electrophoretic mobility or fluorescence, and wherein said step of cleaving includes providing a second antibody binding compound specific for each of said one or more target compounds, each second antibody compound having a sensitizer for generating an active species for oxidizing said cleavable linkage.

15. The method of claim 14 wherein said active species is singlet oxygen and said cleavable linkage is an olefin, a thioether, a sulfoxide, or a selenium analog of the thioether or sulfoxide.

16. The method according to claim 14 or 15 wherein said step of providing includes providing a plurality of from 5 to 100 said antibody binding compounds.

17. The method of claim 16 wherein said mobility modifier consisting of from 1 to 300 atoms selected from the group consisting of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and boron.

18. The method of claim 17 wherein said detection group comprises a fluorescent label or an electrochemical label.

19. A method for determining the presence or absence of one or more target compounds in a sample, the method comprising the steps of:

providing one or more binding compounds specific for each of the one or more target compounds, each binding compound having one or more eTag reporters attached thereto by a cleavable linkage, the one or more eTag reporters of each binding compound being distinguished from those of other binding compounds by one or more physical characteristics;

providing a second binding compound specific for each of the one or more target compounds, each second binding compound having a sensitizer for generating an active species;

combining with the sample one or more binding compounds and a second binding compound for each of the one or more target compounds such that in the presence of a target compounds a complex is formed between the target compound, the one or more binding compounds specific therefor, and the second binding compound specific therefor, and such that the sensitizer of the second binding compound causes the generation of an active species and the cleavage of one or more cleavable linkages to release one or more eTag reporters; and

electrophoretically separating and identifying the one or more released eTag reporters to determine the presence or absence of the one or more target compounds.

20. The method of claim 19 wherein said cleavable linkage is cleaved by oxidation and wherein said active species is singlet oxygen or hydrogen peroxide.

21. The method of claim 20 wherein said active species is singlet oxygen and said cleavable linkage is an olefin, a thioether, a sulfoxide, or a selenium analog of the thioether or sulfoxide.

22. The method of claim 21 wherein said binding compound and said second binding compound are each antibody binding compounds.

23. The method according to claim 19, 20, 21, or 22 wherein said eTag reporter are identified by fluorescence or by an electrochemical label, and wherein said step of providing one or more binding compounds includes providing a plurality of from 5 to 100 said binding compounds.

24. The method of claim 23 wherein said sensitizer generates singlet oxygen upon photoactivation.

25. The method according to 19, 20, 21, or 22 further including, prior to said step of electrophoretically separating, a step of separating said released eTag reporters from any components that interfere with electrophoretic analysis.--